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Blood flow measurements in lower limb arteries using duplex ultrasound

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The increase in blood flow in exercise is to provide more oxygen to tissues. The kinetics of flow at the common femoral artery bifurcation were established in normal subjects together with its relationship with oxygen uptake. Furthermore, the changes in flow were evaluated in patients undergoing superficial femoral artery angioplasty.

After a known anaerobic test (Wingate test), normal subjects underwent a preferential increase in profunda femoris artery flow (ninefold increase), compared with superficial femoral artery flow (fourfold increase), indicating predominantly thigh exercise. The relationship between oxygen uptake and lower limb blood flow was studied before, during and after moderate intensity exercise. Oxygen uptake was measured by mass spectrometry and assessed by breath-by-breath analysis. The rate of increase for limb blood flow, as indicated by the time constant, was faster (28.8 ± 4.4 s; mean ± sem) than oxygen uptake (41.5 ± 7.2 s) at the onset of exercise. This implies that limb blood flow is in excess of the oxygen requirements of muscle and therefore not the critical determinant for oxygen uptake by muscle.

Flow in the lower limb arteries was measured before and after superficial femoral artery angioplasty in 22 patients. In addition, collateral blood flow was estimated using a mathematical model. Follow-up was carried out to 1 year. At 1 month, a significant decrease in profunda femoris artery flow (from 224 ± 84 to 98 ± 43 ml min^{-1}, $P < 0.05$, paired t test) and a marked diminution in collateral flow (from 186 ± 34 to 18 ± 8 ml min^{-1}, $P < 0.05$) was noted with no change in total limb blood flow. As expected, a significant increase in superficial femoral artery blood flow was seen (148 ± 79 to 312 ± 94 ml min^{-1}, $P < 0.05$).

From the studies, it can be seen that non-invasive duplex ultrasound flow measurements can reliably be obtained in the lower limb, allowing the kinetics of flow after exercise and the changes in flow after surgical intervention to be evaluated. This work provides a foundation for the study of oxygen kinetics and limb blood flow in athletes, the elderly and patients with peripheral vascular disease.

John Hunter (1728–1793) is regarded as one of the outstanding anatomists and pathologists that has ever lived. In his collection, which resides at the Hunterian Museum, is a specimen of a medium-sized artery with a narrowing. He realised that this narrowing was due to disease and the flow to that limb would be affected. Optimum treatment of peripheral vascular disease requires the accurate localisation of such arterial lesions and an assessment of their effect on function.

For many years, physiologists have been studying the normal heart and the vascular system. Yet it is only relatively recently that surgeons have been investigating the effects of atherosclerosis on blood flow. The combination of the two disciplines has enormous potential for improving our understanding of vascular haemodynamics and for assessing the outcome of treatment in patients by utilising advances in non-invasive technology to measure flow in the cardiovascular system.

William Harvey (1628), a physician at St Bartholomew's Hospital, was the first to measure blood flow. By measuring heart rate and, in post-mortem subjects, left ventricular diastolic volume, he estimated cardiac output to be 3 litres/min. In 1733 the Reverend Stephen Hales investigated the dynamics of the circulation. He measured the circulation rate by estimating the velocity in veins and arteries and introduced the concept of peripheral resistance in arterioles. Since then there have been many

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methods to measure blood flow, all with a variable degree of accuracy. The majority of techniques are invasive and thus do not lend themselves to repeated flow measurements, particularly after exercise or a surgical procedure. Duplex ultrasound is non-invasive and therefore has the advantage of allowing repeated measurements of flow under a variety of conditions.

Duplex ultrasound

Satomura and Kanebo *(1)* realised that continuous wave Doppler ultrasound could be used to detect blood flow. It was noted that when a beam of ultrasound passed through flowing blood, the moving particles (predominantly red blood cells) caused a shift in the frequency of the reflected sound which could be calculated from the Doppler equation:

$$f_d = \frac{f_t 2v \cos\theta}{c}$$

where f_d = Doppler shift frequency, f_t = transmitted frequency, v = velocity of scattering particles, θ = incident Doppler angle, and c = velocity of sound in blood.

Subsequent work established that an ultrasound beam could be produced and detected by a piezoelectric ceramic crystal and the resulting frequency shift processed to produce an audible signal.

An objective assessment of the degree of ischaemia could be made by using this audible signal to estimate systolic blood pressure in a distal vessel. The ratio of the ankle-to-brachial systolic pressure at rest and after exercise has subsequently become one of the simplest methods of distinguishing between normal subjects and those with impaired vascular perfusion *(2)*. Further analysis using signal processing can produce a visual record (Fig. 1).

Concurrent with the use of ultrasound to detect flow by the Doppler effect, real-time B-mode ultrasound was being applied to image blood vessels and atheroma. Studies of the abdominal aorta showed that B-mode ultrasound was more accurate than either clinical examination, plain radiography and aortography in the diagnosis of abdominal aortic aneurysms. It also provided evidence of dissection, intraluminal thrombus and aneurysmal involvement of the iliac arteries *(3)*. Examination of grafts could indicate the presence of dilatation, seromas and false aneurysms *(4,5)*.

Therefore, the combination of a B-mode image with a pulsed Doppler trace (duplex sonography) could not only visualise anatomy, but also obtain quantitative information relating to blood flow *(6)*. It also allowed the observer to pinpoint accurately the origin of the Doppler signal and in turn provide a non-invasive technique that can be used to obtain morphological as well as haemodynamic information.

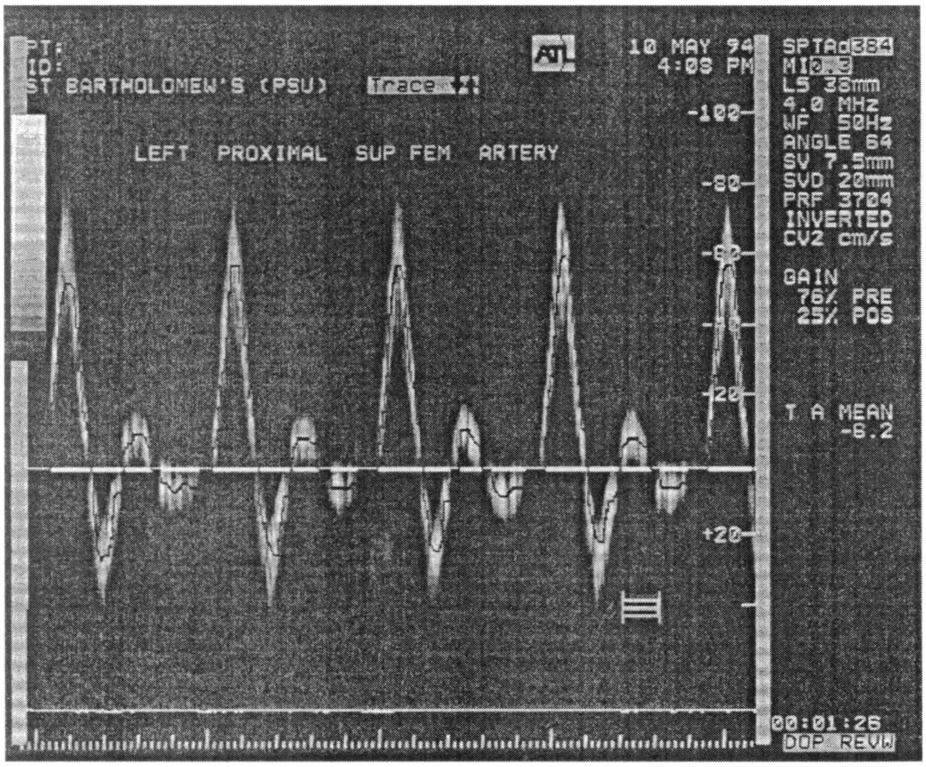

Figure 1. Spectral Doppler trace of the proximal superficial femoral artery, with time in seconds on the x-axis and velocity in cm/s on the y-axis. The waveform is quadriphasic with forward flow in systole, followed by reverse flow in early diastole, a small forward flow component in mid-diastole and finally a small reverse flow component in late diastole.

The potential that duplex ultrasound could estimate volumetric blood flow, ie flow in ml min^{-1} and not just velocity in cm/s as an index of flow, was realised over a decade ago *(5)*. Yet it is only recently, with advances in integral software, that instantaneous flow measurements have been possible. One of the first published results of flow measured by duplex ultrasound was from Lewis *et al.* *(7)*. He measured flow in the human common femoral artery (CFA) and found that flow was in keeping with more invasive techniques—350 ± 141 ml min^{-1} (mean $\pm$ SD).

One of the interesting areas of fluid dynamics is the flow distribution at bifurcations. It was noted by Ferguson and Roach *(8)* that vascular bifurcations produce local disturbances of blood flow. The haemodynamic forces related to these disturbances may play an important role in the pathogenesis of focal vascular lesions such as atherosclerosis, intimal cushions and human intracranial aneurysms. Furthermore, it has been well known to vascular surgeons that at the common femoral artery (CFA) bifurcation into the superficial femoral artery (SFA), and profunda femoris artery (PFA), it is the PFA that is relatively spared of atherosclerosis and it is the SFA which is more commonly affected by disease. The PFA is the main artery to the thigh, whereas the SFA is the main artery to the lower leg with no major branches in the thigh.

Duplex ultrasound allows flow in all three vessels to be measured at similar points in the same individual. Therefore, it allows analysis of the distribution of flow beyond the CFA into the SFA and PFA under different physiological and pathological conditions such as at rest and after exercise in normal subjects and in patients with intermittent claudication. Furthermore, it may have the ability to measure flow during exercise.

Blood flow in normal subjects

The sum of the PFA and SFA flow should approximate to CFA flow, as there are no other major branches from the CFA. In a small proportion of subjects, the circumflex vessels come directly off the CFA and therefore the sum of the CFA and PFA flow would theoretically underestimate the CFA flow in some individuals. Although the circumflex vessels can be visualised by duplex ultrasound, they are probably too small for flow to be measured with any degree of accuracy. The results of a group of normal individuals' flow in all three vessels is shown in Fig. 2. The mean discrepancy between the sum of the flow in the SFA and PFA and the flow in the CFA, in these subjects, was 40 ± 9 ml min^{-1}. This figure probably reflects the flow in both circumflex vessels, together with any observer error.

Although total limb blood flow using invasive methods has been measured after exercise, the changes in blood flow distribution, beyond the CFA, to the thigh and calf have not previously been addressed. Furthermore, evaluation of the time taken for flow in all three vessels to return to normal will allow the magnitude of the challenge of the exercise to a particular muscle group to be estimated. In addition, it may provide a baseline for the subsequent study of flow at the CFA birfurcation in patients with peripheral vascular disease. The method of assessing how quickly flow returns to normal is the time constant τ (time taken for the flow to return to two-thirds of its final value). This value is calculated by the exponential decline in flow after exercise.

The exercise evaluated in this study was the Wingate test. This well-known test, is a 30 s bicycle test which has been shown to cause marked fatigue in a short space of time by energy expenditure, which is principally

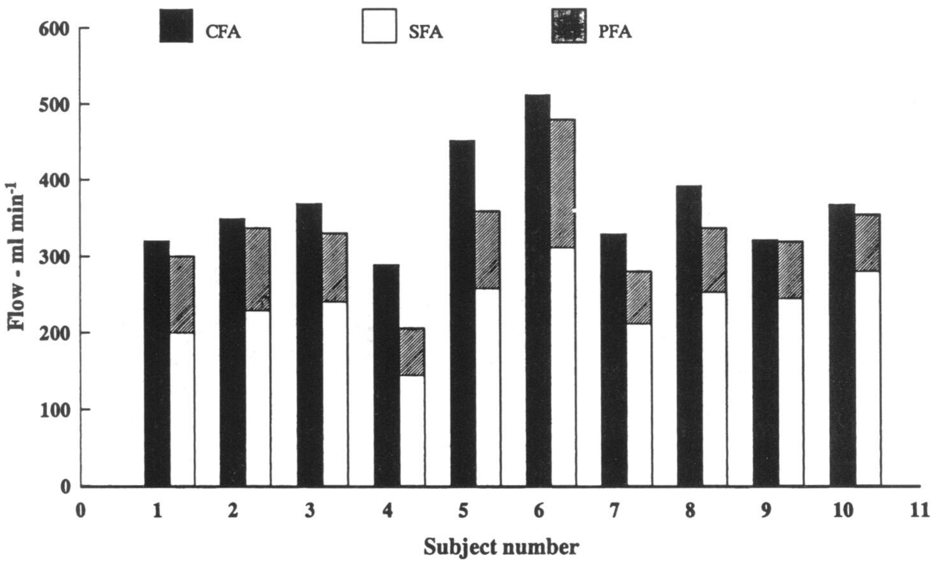

Figure 2. Flow in the CFA, SFA and PFA in ten healthy subjects. The SFA and PFA flow have been stacked together to show the flow discrepancy with that of the CFA.

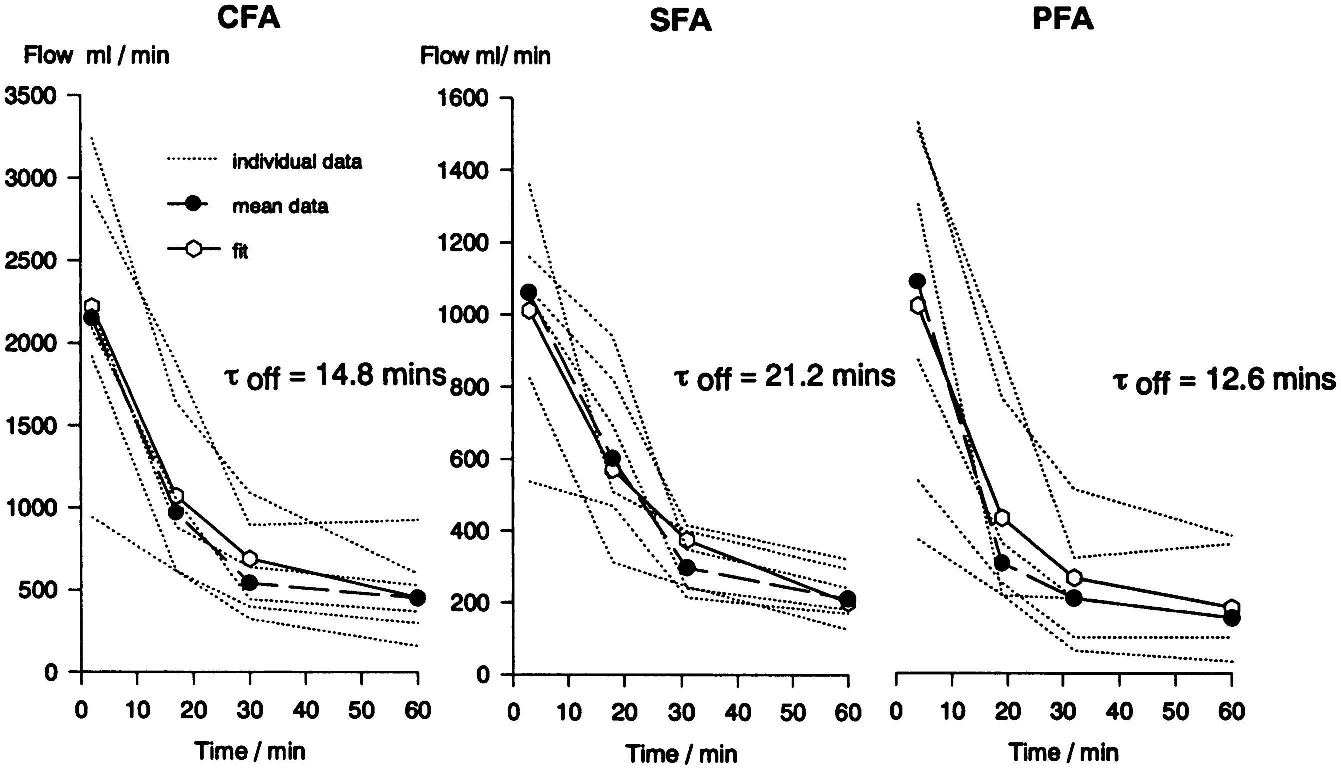

Figure 3. Recovery kinetics of flow in the CFA (common femoral artery), SFA (superficial femoral artery) and PFA (profunda femoris artery). Note the prolonged time constants at the off-transient (τ_{off}).

anaerobic *(9)*. This sort of high-intensity exercise causes a marked increase in blood lactate levels, which remain significantly elevated for 1 h after exercise *(10)*. Consequently, there is likely to be a significant increase in limb blood flow during the test, which should remain elevated for some time after exercise. Furthermore, it is anaerobic metabolism that is predominant in ischaemic pain and therefore the recovery of flow is analogous to the changes in blood flow during claudication.

In fit normal subjects, approximately one-third of the flow in the CFA (314 ± 79 ml min^{-1}) at rest was distributed to the PFA (99 ± 18 ml min^{-1}), and two-thirds of the flow to the SFA (219 ± 65 ml min^{-1}). The mean CFA flow increased some sevenfold to 2150 ± 398 ml min^{-1} at the end of the exercise. The increase in PFA flow (9.1fold) was significantly greater than the increase in SFA flow (4.4fold; $P = 0.036$, Wilcoxon test). The time constants were surprisingly long, averaging 14.8, 21.2 and 12.6 min, respectively, in the CFA, SFA and PFA; that is, the longest time constant was evident in the SFA (Fig. 3). This preferential increase in flow to the thigh musculature presumably reflects the greater contribution of the thigh muscles to the total increase in metabolic rate. Consequently, the blood flow to metabolic rate ratio may actually be lower in the muscles perfused by the SFA and have a greater 'anaerobic' contribution to the energy transfer in these muscles.

The study demonstrated that the dynamics of the changes in blood flow after a high-intensity exercise test, before and beyond the bifurcation of the common femoral artery, can be determined. Even short-duration high-intensity (anaerobic) exercise can cause marked haemodynamic changes that take up to 1 h to return to baseline values. This prolongation of the recovery kinetics of femoral arterial flow probably reflected the sustained effect of vasodilator metabolites. Ischaemic pain is also induced by the limitations of anaerobic metabolism. Therefore, the study provides a basis for establishment of the recovery kinetics of lower limb blood flow in claudicants. The speed at which blood flow returns to normal may well be an objective measurement of the degree of claudication.

Oxygen uptake and blood flow

It is accepted that it is the limited blood supply to muscle as a result of increased demand during exercise which leads to ischaemic pain or intermittent claudication. However, this relationship, between oxygen uptake VO_2 and limb blood flow, has not been established in normal subjects. There remains a considerable controversy in the physiology literature as to whether at the onset of exercise, oxygen uptake is limited by the metabolic processes of muscle or the availability of O_2, ie limb blood flow *(11,12)*.

Normal subjects are rarely in a steady metabolic state, except for certain phases of sleep or deliberate repose. This 'steady state' is known as the period in which cardiac output and/or oxygen uptake (VO_2) are at a constant level. It occurs at rest and also during the period of exercise, after the onset, in which cardiac output or oxygen uptake has plateaued (Fig. 4). In the steady state, VO_2 increases as a linear function of work done during muscular

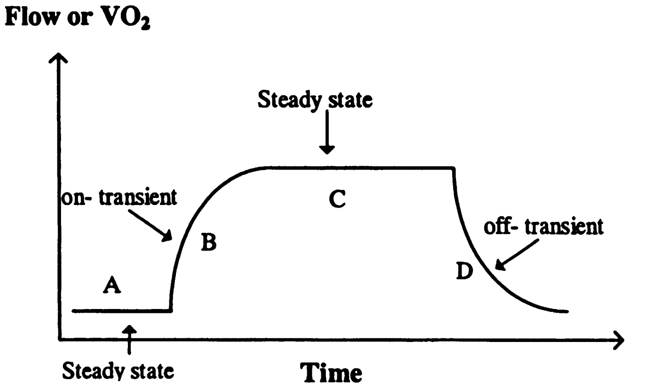

Figure 4. The graph shows the different components of the increase in flow or VO_2 before, during and after exercise. A, steady-state response at rest before exercise; B, increase at the beginning of exercise, or the 'on-transient'; C, period of exercise in which flow or VO_2 remains constant or the 'steady state'; D, decrease to resting values at the termination of exercise or the 'off-transient'.

exercise. However, it is the non-steady metabolic state that is the more usual condition and, furthermore, it contains the physiological information regarding the particular system's control characteristic. The on-transient is the termed used to describe the period of increase at the onset of exercise. The off-transient similarly describes the exponential decrease to resting values, Fig. 4. Both these periods are also known as the 'non-steady state'.

The non-steady state profile of VO_2 has been shown to be mono-exponential towards its steady state during moderate exercise *(12)*. The time constant of this VO_2 response (O_2) is longer in sedentary than in trained subjects *(13)*, and is as much as threefold longer in elderly sedentary subjects *(14)*. The time constant in patients with intermittent claudication remains unknown. As exercise begins, muscle oxygen uptake increases immediately. As the kinetics of oxygen uptake at the lungs are similar to that in limb muscle but only different in time, oxygen uptake at the lung can be used to delineate the on-transient of oxygen uptake at the peripheral muscle *(15)*.

A difficulty in establishing a true relationship between VO_2 and limb blood flow has been the inability to measure changes in blood flow to the working muscle *during* the on- and off-transients of a period of exercise. Therefore, the dynamics of cardiac output have been used as an index of the dynamics of limb blood flow to the working muscles during the on- and off-transient of constant load exercise. If the time constant for limb blood flow is shorter than VO_2 throughout the on-transient, then this is incompatible with blood flow being the critical determinant of VO_2 dynamics. Instantaneous measurements using duplex ultrasound during this on-transient could establish a direct relationship between VO_2 and limb blood flow.

For this study, subjects isolated exercise of the quadriceps in a semi-recumbent posture, stretching rubber bands of length and recoil characteristics sufficient to induce the required increase of metabolic rate and limb blood flow. They were arranged as stirrups

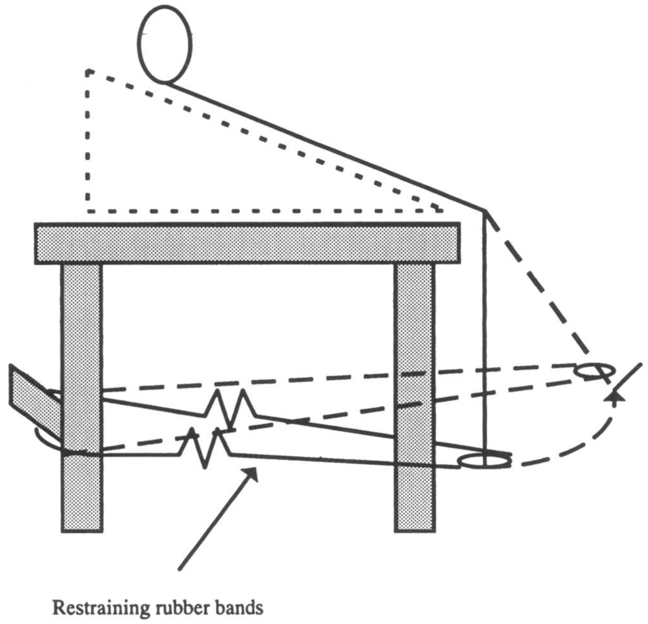

Figure 5. Schematic representation of the 'quadriceps isolation' protocol. The legs are extended alternately against restraining rubber bands, with wooden stops setting the excursion range and a metronome setting the cadence. Note that the legs are returned passively to the starting position by the elastic recoil of the bands. The semi-recumbent posture provides access to the common femoral artery for the Doppler probe.

placed over the dorsal surface of the foot for alternate quadriceps contractions (Fig. 5). Subjects were asked to contract their quadriceps muscle. After the active contraction phase, the return to the resting position is achieved mainly through the device recoil rather than by contraction of the antagonist muscles, thereby 'isolating' the work to the quadriceps muscles. Blood flow and oxygen uptake data were collected throughout the exercise. The subjects exercised while breathing through a mouthpiece allowing oxygen uptake to be analysed using a mass spectrometer.

The evidence from the study suggested that the time constant of limb blood flow, at the on-transient (28.4 ± 4.4 s), was significantly faster than that for O_2 (41.5 ± 7.2 s), $P < 0.05$ Mann–Whitney test. CFA blood flow was significantly slower at the off-transient (40.8 ± 3.8 s) than at the on-transient (for high-intensity exercise, $P < 0.05$ Mann–Whitney test), whereas there was no significant difference in VO_2 at the on- and off-transients.

Owing to the difficulties of measuring blood flow using other techniques at the onset and offset of exercise; cardiac output had previously been used. The on-transient for cardiac output had been shown to be shorter than that of O_2 *(16)*. Therefore, both sets of data support the theory that O_2 is not critically determined by O_2 delivery to the muscle during moderate exercise. Therefore, blood flow is probably in excess of oxygen delivery in normal subjects. The relationship between the two has not been established in patients with peripheral vascular disease. We know from studies such as the Framingham study that some subjects have significant stenosis in major arteries in the lower limb, such as the SFA, and yet have no symptoms *(17)*. It may be that they have a more established mode of extraction of oxygen from the same limited blood flow or that for some reason their blood flow requirements during exercise are not limited to the same degree, possibly via a collateral pathway. Certainly, the establishment of the relationship between blood flow and oxygen uptake in both symptomatic and asymptomatic subjects with peripheral vascular disease will aid in the evaluation of the subject.

Collateral blood flow

One of John Hunter's more famous operations was for the treatment of popliteal aneurysm. In a 36-year-old coachman, he tied off the superficial femoral artery at its origin. The patient went on to live into his old age. The operation, the first of its kind, demonstrated how the collateral circulation could maintain viability of a major limb. The collateral circulation is composed of small blood vessels which form highly resistant pathways. It is well accepted that in the presence of a significant stenosis to a major limb artery the parallel collateral pathway can allow the maintenance of a normal blood supply to the peripheral vascular bed, at least under resting conditions. However, with the increasing demands of exercise, the resistance in the collateral pathway will usually prevent a sufficient increase in blood flow to meet the demands of the exercising muscle and symptoms of ischaemia will ensue. It is not known why some subjects develop intermittent claudication and others remain asymptomatic in the presence of similar stenoses. The hypothesis that there is development of a sufficient collateral blood supply in the asymptomatic subjects to meet the increased requirements of exercise has been put forward.

The stimulus for the development of collateral circulation has been considered to be either the pressure gradient across the vascular bed, or tissue hypoxia *(18)*. Exercise causes both ischaemia and an increased pressure differential in an obstructed limb and may be the stimulus for continued growth of collaterals. Clinically, whether the differential in pressure or the hypoxia of the muscle is important, exercise is of proven therapeutic value in patients with intermittent claudication *(19)*.

Quantification of flow is difficult owing to the very nature of these collateral channels. Its importance was realised as early as 1944, when Green *et al.* *(20)* described it as the "rate of flow which actually passes from the collateral bed across the anastomotic channels and through the cognate bed when the cognate artery is occluded". The first to provide any objective quantitative data of the collateral pathway were Sumner and Strandness *(21,22)*. Their mathematical model, based on an electrical circuit, assumes that the relationship between pressure and blood flow is linear. In addition, mean venous pressure is assumed to be zero as pressure and flow measurements are taken in the supine position. They measured collateral resistance in a series of patients

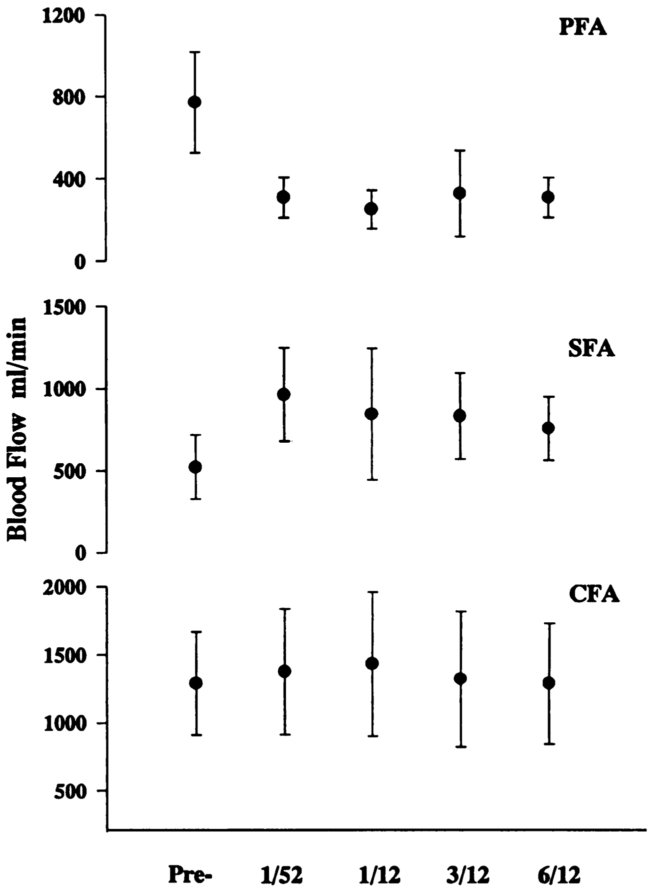

Figure 6. Blood flow changes in the CFA (common femoral artery), SFA (superficial femoral artery) and PFA (profunda femoris artery), before (pre-) and (1 week, 1/52; 1 month, 1/12; 3 months, 3/12; and 6 months, 6/12) after angioplasty. The increase in SFA flow and decrease in PFA are statistically significant ($P < 0.05$, paired t test with Bonnferroni's correction).

with an occlusion of the superficial femoral artery. They showed that the collateral resistance increased after exercise to a greater extent than in normal subjects. They were unable to calculate collateral blood flow because they had no method of estimating CFA, SFA and PFA blood flow at similar time points.

In a group of patients undergoing SFA angioplasty, measurements of flow and pressure were made non-invasively in the CFA, SFA and PFA. Measurements were taken before and after SFA angioplasty and at 1, 3 and 6 months. It was noted, as have other authors, that there was no overall improvement in total limb blood flow as CFA flow remained unchanged *(23)*. All patients reported an improvement in symptoms of intermittent claudication. The improvement in symptoms was thought to be because of a statistically significant improvement in SFA blood flow with a corresponding decrease in PFA blood flow (Fig. 6). Blood was therefore passing through a pathway of decreased resistance compared with before SFA angioplasty. Collateral flow was calculated using the mathematical model. It was noted that, at rest, collateral flow decreased from 186 ± 34 ml min^{-1} before angioplasty to 18 ± 18 ml min^{-1} and then 11 ± 9 ml min^{-1} at 1 week and 1 month after angioplasty. Measurements after exercise showed that collateral flow fell from 258±49 ml min^{-1} to zero after angioplasty; the results being the same at 1 month.

Although this study calculated not only the changes in blood flow distribution after angioplasty and the collateral blood flow, the latter is only a reflection of the true collateral flow as the model was too simplistic. The relationship between flow and pressure is non-linear in both the arterial and capillary circulation. This is because there is local disturbance of flow in arteries affected by atherosclerosis, and in the capillary circulation there exists a critical closing pressure owing to the collapsible nature of capillaries. Despite these flaws the model confirms what surgeons and radiologists have thought for some time, that collateral flow diminishes after angioplasty. Accurate haemodynamic data on collateral flow changes after surgery, such as femoropopliteal bypass, and angioplasty would require the advent of non-linear equations that would account for the relationship between pressure and flow within the cardiovascular system. The advent of more complex computer modelling of the peripheral vasculature may well be able to predict accurately the outcome of flow changes after surgery or angioplasty *(24)*. Such models will still have to rely on *in vivo* measurements of flow in individual arteries.

To summarise, although blood flow measurements using duplex ultrasound have been possible for some time, it has been the resolution of the machines that has prevented reliable measurements from being obtained. With the advent of fourth generation duplex scanners, improved resolution has allowed accurate measurements to be taken, provided a meticulous technique is adhered to. Flow measurements compared with a phantom flow model using a starch/alcohol mixture as a blood analogue have shown a close correlation ($r = 0.99$) with a coefficient of variation of 12%. With ever developing software and improved resolution, such errors may become of less importance. However, a rigid protocol needs to be adhered to by well-trained and experienced duplex ultrasonographers to obtain an acceptable observer error. For these studies the observer error was 13%, 15% and 21% for the CFA, SFA and PFA, respectively *(25)*.

Instantaneous non-invasive assessment of flow in ml min^{-1} has improved our understanding of the haemodynamic and physiological changes at the common femoral artery bifurcation in normal subjects before and after exercise, provided an insight into the major changes in flow in patients who have undergone SFA angioplasty and a quantitative prediction of collateral blood flow. The methodology should enable further evaluation of the haemodynamic changes induced in blood vessels and an objective assessment of outcome of treatment as it is the improvement of flow and the delivery of oxygen to the ischaemic tissues that is the aim. Already, duplex ultrasound is an established tool for the assessment of patients with peripheral vascular disease and there is no reason why these additional measurements, with the further advances in resolution, become part of normal clinical practice rather than measurements taken in laboratory settings.

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